Diabetes Mellitus

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Introduction

- Diabetes Mellitus
  - A group of metabolic disorders characterized by chronic hyperglycemia from lack of insulin production, resistance to insulin action, or a combination of both.
  - Associated with dysfunction of multiple organ systems including the kidneys, eyes, nerves, heart, and blood vessels.

Diabetes Classification

- Type 1 Diabetes—5-10% of cases
  - Absolute deficiency of insulin secretion
    - Autoimmune—cell-mediated beta-cell destruction
      - Markers of immune destruction: GAD (glutamic acid decarboxylase), islet cell , insulin, IA-2 and IA-2B antibody positivity.
      - Strong HLA association (DQ and DR)
      - Genetics background + some ? environmental trigger
      - Can be prone to other autoimmune disorders
        - Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, celiac sprue, myasthenia gravis, pernicious anemia, etc.
    - Idiopathic
      - Insulinopenic and prone to ketoacidosis
      - No evidence of autoimmuity.
      - Most patients are of African or Asian ancestry.

Diabetes Classification

- Type 1 DM
  - Patient profile
    - Most diagnosed < 30 y/o; 20% diagnosed after age 30.
    - Caucasian race or population with substantial white genetic admixture (including African Americans)
    - Significant weight loss despite polyphagia (severe catabolic state)
    - Thin body habitus
    - Presence of other autoimmune diseases
    - Ketoacidosis prone

Diabetes Classification

- Type 2 Diabetes—90-95% of cases
  - Combination of insulin resistance and inadequate compensatory insulin secretion.
    - Insulin resistance
      - Obesity (particularly abdominal/visceral)
      - Habitual inactivity
      - Ketoacidosis less common but can occur with severe stressors or new onset DM.
    - Insulin secretory defect
      - Beta-cells incapable of compensating for insulin resistance.
      - Progressive loss of beta-cell function with time.
  - Strong genetic predisposition
    - Nearly 100% concordance among monozygotic twins (compared to 50% in autoimmune type 1 DM)
    - Genetics are more complex (polygenic)

Diabetes Classification

- MODY—Maturity-Onset Diabetes of the Young
  - Associated with monogenic defect in beta-cell function.
    - Autosomal dominant
    - Minimal or no defects in insulin action.
  - Hyperglycemia generally before age 25
- Diseases of the exocrine pancreas
  - Generally due to extensive/diffuse injury to the pancreas resulting in impaired beta-cell function
  - Pancratitis, trauma, infection, pancreatectomy, pancreatic carcinoma, cystic fibrosis, hemochromatosis

Diabetes Classification

- Gestational DM
  - 4% of all pregnancies in U.S.
- Endocrinopathies
  - Excessive production of insulin counter-regulatory hormones
    - Growth hormone—acromegaly
    - Cortisol—Cushing's syndrome
    - Catecholamines—pheochromocytoma
    - Glucagon—Glucagonoma
  - Others
    - Hyperthyroidism, aldosteronoma
- Drugs
  - Nictotinic acid, glucocorticoids, alpha-interferon, diazoxide, beta-blockers, thiazides, dilantin, pentamadine

Screening for Type 2 DM

- Risk factors for type 2 DM
  - Age >/= 45
  - Overweight (BMI >/= 25 kg/m2)
  - Fhx of diabetes
  - Habitual physical inactivity
  - Race (African-American, Hispanic, Native American, Asian American, Pacific Islander)
  - Hx of Impaired Fasting Glucose or Impaired Glucose Tolerance (Collectively, pre-diabetes)
  - Hx of gestational DM or baby weighing >9 lbs
  - Hypertension
  - Hyperlipidemia
  - Polycystic Ovary Syndrome
  - Hx of vascular disease
- Who and When to Screen?
  - Q 3 years beginning at age 45.
  - Consider testing at younger age or more frequently in overweight patients who have one or more other risk factors.

Diagnostic Criteria--2004

	Normo-glycemia	Pre-Diabetes	Diabetes
Fasting Plasma Glucose (FPG)	**<100 mg/dl** (Previously <110 mg/dl)	100-125 mg/dl (Impaired Fasting Glucose)	FPG ≥ 126 mg/dl
2-hour Plasma Glucose	<140 mg/dl	140-200 mg/dl (Impaired Glucose Tolerance)	≥ 200 mg/dl
Casual plasma glucose			≥ 200 mg/dl with symptoms

A diagnosis of diabetes must be confirmed on a subsequent day by any of the above tests in the absence of unequivocal hyperglycemia. FPG is preferred because of ease of administration, convenience, acceptability to patients, and lower cost. Fasting is defined as at least 8 hours of no caloric intake. 2-hour testing involves an equivalent of 75 g anhydrous glucose dissolved in water.

Treatment of Type 2 DM

- Diet, Exercise, Patient Education
- Control of hyperglycemia
  - Treatment Goals
  - Medication choices
- Control of hypertension
  - Treatment Goals
  - Preferred agents
- Control of hyperlipidemia
  - Treatment Goals
- Screening/Treatment of Complications

Hyperglycemia--Treatment Goals

- ADA 2004
  - HbA1C < 7%
  - “More stringent goals can be considered in individual patients…However the absolute risks and benefits of lower targets are unknown”
- American Association of Clinical Endocrinologists
  - HbA1C < 6.5% based on epidemiological data showing reduced complications with lower HbA1C.
- Goals must be modified to fit patient circumstances (e.g. risk of hypoglycemia, age, comorbidities, etc.) must be taken into account.

Insulin Secretagogues

- Sulfonylureas
  - Mechanism
    - Bind to sulfonylurea receptor next to ATP-sensitive K+ channel leading to insulin release
  - Examples: Glyburide, Glipizide, Glimepiride
  - Contraindications
    - Sulfa allergy
    - Type 1 DM, DKA
  - Adverse effects: Hypoglycemia, hypersensitivity, weight gain
    - Increased hypoglycemia with Glyburide due to active, renally-cleared metabolites (use with caution in renal insufficiency and elderly)
- Meglitinides
  - Mechanism: Binds to site on beta-cell membrane leading to insulin release
  - Rapid oral absorption and elimination for use in controlling post-prandial hyperglycemia.
  - Examples: repaglinide, Nateglinide
  - Contraindications
    - Type 1 DM, DKA
  - Adverse effects: Hypoglycemia, weight gain

Insulin Sensitizers

- Glucophage
  - Mechanism: Biguanide drug which primarily increases insulin sensitivity at the level of the liver (decreases hepatic glucose production)
  - Contraindications/Precautions
    - Cr ≥ 1.4 in females and ≥ 1.5 in males
    - CHF requiring pharmacologic treatment
    - Acute or chronic metabolic acidosis
    - Acute hypoxic state
    - Liver disease
    - Hold for 48 hrs subsequent to IV contrast exposure; reinstitute with confirmation of normal renal function.
    - Use with caution in >/= 80 y/o. Follow creatinine clearance.
  - Side Effects
    - Lactic acidosis—rare (0.03 cases/1000 pt years) but deadly (50% mortality)
    - GI side effects—Nausea, diarrhea, altered taste. Rarely persist with continued use. Less when taken with meals and when dose is titrated slowly.
  - Advantages
    - **Weight neutral**
    - No hypoglycemia with monotherapy.
    - Favorable impact on lipids
    - Possible cardiovascular risk reduction

Insulin Sensitizers

- Thiazolidinediones (TZDs)
  - Mechanism—Bind to PPAR-gamma receptor in peripheral tissues mainly skeletal muscle
    - Result in expression of cell-surface glucose transporters.
  - Cautions
    - Not recommended in NYHA Class III/IV CHF
    - May cause fluid retention and precipitate CHF
    - May cause mild anemia (? Dilutional effect)
    - Associated with weight gain
    - Liver toxicity seen in older TZD (troglitazone) but not with newer agents; recommended to check LFTs q 2 mo for 1st year of use.
  - Advantages
    - No hypoglycemia
    - Possible improvement in vascular function

Alpha-Glucosidase Inhibitors

- Mechanism
  - Reversible inhibitors of the alpha-glucosidase enzyme on intestinal brush border which delays digestion/absorption of ingested carbohydrate
  - Primarily impacts post-prandial blood glucose
- Drugs: Acarbose (precose) miglitol (Glyset)
- Adverse effects
  - Flatulence, bloating (high rate of discontinuation)
- Contraindications
  - Major GI disorders including inflammatory bowel disease, chronic ulcers, malabsorption, or intestinal obstruction.

Insulin

- Profile
  - Multiple forms with different pharmacokinetic profiles
  - No maximum dose
  - No evidence for harmful effect on cardiovascular outcomes
  - Increased potential for hypoglycemia

Pharmacokinetics of Insulin Preparations[1]

Insulin Preparations	Onset of Action	Peak Action	Duration of Action
Lispro/Aspart --Insulin monomer	5-15 minutes	1-2 hours	4-6 hours
Human Regular --hexameric	30-60 minutes	2-4 hours	6-10 hours
Human NPH/Lente	1-2 hours	4-8 hours	10-20 hours
Ultralente	2-4 hours	Unpredictable	16-20 hours
Glargine	1-2 hours	Flat	24 hours

*The time course of action of any insulin may vary in different individuals, or at different times in the same individual. Because of this variation, time periods indicated are considered general guidelines only.

1 From Endocrinology and Metabolism Clinics Volume 30 • Number 4 • December 2001

Insulin Strategies

- "Split-Mix"—Twice daily NPH/Regular
  - Advantage: Simplicity; two injections
  - Disadvantages
    - Hypoglycemia from AM NPH if lunch is delayed
    - Hyperglycemia after lunch due to lack of pre-lunch insulin
    - Hypoglycemia overnight due to peaking of dinner-time NPH
    - Hyperglycemia in AM due to waning of dinner-time NPH
  - Recommendations
    - Does not reproduce physiologic insulin production
    - If using this strategy, give evening NPH at bedtime to minimize nocturnal hypoglycemia and AM hyperglycemia.

Insulin Strategies

- “Basal-Bolus” approach—Glargine insulin with pre-meal lispro/aspart.
  - Advantage: More closely approximates normal insulin secretion
  - Disadvantage: QID injections and frequent FSBG monitoring required to tailor doses.

Early AM Hyperglycemia—Possible Causes

- Dawn phenomenon
  - Rise in BG in early morning as the result of pulsatile release of insulin counter-regulatory hormones (growth hormone and cortisol)
- Somogyi phenomenon
  - Period of morning hyperglycemia following nocturnal hypoglycemia.
  - Studies have failed to show that this occurs commonly.
- NPH insulin given at dinner with waning effect by AM
- Late night snacking

Chronic Complications—Ophthalmopathy

- Diabetic Ophthalmopathy
  - Leading cause of blindness in U.S.
  - Non-proliferative diabetic retinopathy (NPDR)
    - Earliest stage
    - Microaneurisms and intraretinal “dot and blot” hemorrhages
    - Macular edema or hard exudates at/near macula can cause visual impairment
  - Proliferative diabetic retinopathy (PDR)
    - Nonperfusion of retina→angiogenesis→growth of abnormal new vessels extending onto inner surface of retina or into vitreous cavity.
    - Substantial risk for rupture→hemorrhage or retinal detachment.
    - Treated with panretinal photcoagulation.
- Screening
  - Type 1—1st screening within 3-5 years from onset of DM and annually thereafter or at the discretion of the eye care provider.
  - Type 2—1st screening at time of diagnosis of DM and annually thereafter or at the discretion of the eye care provider.
- Prevention
  - Glycemic control
  - HTN control
- Referral to ophthalmologist
  - Any level of macular edema, severe NPDR, or any PDR needs prompt referral.

Chronic Complications—Nephropathy

- Diabetic Nephropathy
  - Leading cause of ESRD in US
  - 30-40% of type 1 patients and 5-10% of type 2 patients will develop renal insufficiency.
    - Some type 2 patients may have nephropathy shortly after diagnosis due to delay in diagnosis.
- Screening
  - Earliest marker is microalbuminuria
    - Also a marker of cardiovascular disease
  - Screen for microalbuminuria at the time of diagnosis of type 2 DM and 5 years after onset of type 1 DM and annually thereafter.
  - Preferred screening test is from a random spot urine (accurate and convenient)
- Prevention
  - Glycemic control
  - HTN control
    - In type 1 patients with any degree of albuminuria ACE-I shown to delay progression.
    - In type 2 patients with microalbminuria, ACE-I and ARBs shown to delay progression.
    - In type 2 patients with macroalbuminuria and renal insufficiency, ARBs have been shown to delay progression.
- Nephrology Referral
  - GFR < 60 or difficulties with HTN or hyperkalemia control.

Chronic Complications—Neuropathy

- Types of Neuropathy
  - Sensory
    - Pain/paresthesias in feet particularly at night
    - Numbness in “stocking and glove” distribution
      - High risk for foot ulceration
  - Autonomic
    - Cardiovascular: resting tachycardia, painless MI, orthostasis
    - GI: esphageal dysfunction, gastroparesis, diabetic diarrhea, constipation, fecal incontinence
  - Genitourinary
    - ED, retrograde ejaculation, neurogenic bladder
  - Other
    - “gustatory” sweating, heat intolerance

Chronic Complications—Neuropathy

- Screening
  - History and exam
  - Comprehensive foot exam annually; visual inspection at each visit
- Prevention
  - Glycemic control
  - Appropriate foot care
- Referral to specialist care
  - High risk for foot ulceration

Chronic Complications—Cardiovascular Disease

- Prevention
  - Blood pressure control
    - Target <130/80
    - In diabetic patients older than 55 without HTN but with another cardiac risk factor (including albuminuria), ACE-I may reduce risk of CV events.
  - Lipid management
    - LDL <100 is primary goal in all patients aside from those with severely high TG.
    - Consider use of –statin
  - Antiplatelet therapy
    - ASA (low doses effective) in all patients with known cardiovascular disease.
    - ASA for primary prevention in all diabetics over the age of 40 or who have additional cardiac risk factors.
    - Other antiplatelet agents may be an alternative for those with aspirin allergy with high cardiovascular risk.
    - No aspirin if younger than 21 years old due to increased risk of Reye's syndrome.
  - Smoking cessation

Chronic Complications—Cardiovascular Disease

- Screening
  - Risk factor assessment at least annually
  - Screening/diagnostic cardiac studies based on risk status and/or symptoms.

Question 1

- All of the following are risk factors for type 2 DM except:
  - A) BMI >25
  - B) Physical inactivity
  - C) Proteinuria
  - C) Native American ancestry
  - D) Polycystic Ovary Syndrome

Question 2

- The following is true of the thiazolidinedione class of drugs (pioglitazone and rosiglitazone) except:

A) Primary site of action is the liver
B) Increases insulin sensitivity
C) Have delayed onset of maximum action
D) May be used in combination therapy with Metformin
E) Carry low risk for hepatic injury

Question 3

- All of the following are contraindications to the use of glucophage except:
  - A) History of lactic acidosis
  - B) Male with Cr 1.6
  - C) Type 2 DM with severe CHF
  - D) Concurrent use with thiazolidinedione
  - E) History of alcoholic cirrhosis

Question 4

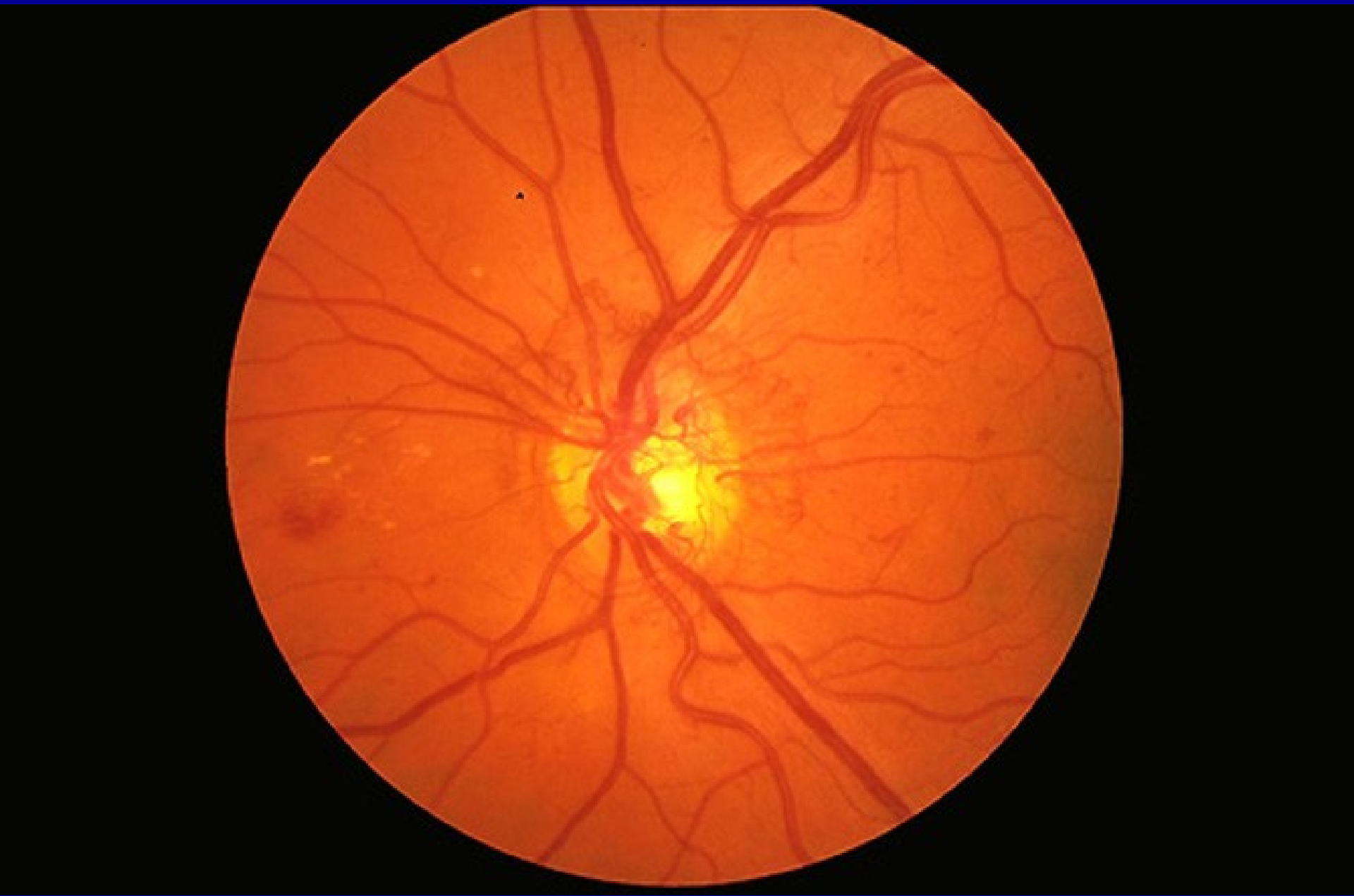
- All of the following are true regarding albuminuria except:
  - A) Risk factor for cardiovascular disease
  - B) The earliest indicator of diabetic retinopathy
  - C) Rarely seen in type 2 DM of < 5 years duration
  - D) Progression can be delayed by ACE-I or ARB therapy

Question 5

- Diabetes may be diagnosed by all except the following (with repeat confirmatory test):
  - A) Elevated fasting blood glucose
  - B) Elevated HbA1C
  - C) Abnormal response to 75gm OGTT
  - D) Presentation in acute diabetic ketoacidosis

Question 6

- A 45 y/o M with type 2 DM presents for initial evaluation. BP is 135/85 and HbA1C is 9.5%. Funduscopic exam reveals the following. What is the best course of action?



Question 6

- A 45 y/o M with type 2 DM presents for initial evaluation. He has not had ongoing medical care. BP is 135/85 and HbA1C is 9.5%. Funduscopic exam reveals the following. What is the best course of action?
  - A) Intensify glycemic control and follow closely.
  - B) Intensify BP control with addition of Ace-I and follow up in 1 month.
  - C) Stop ASA therapy
  - D) Prompt referral to ophthalmologist